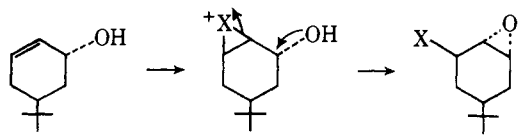
Conformational and Stereochemical Control of an Unprecedented Neighboring Group Participation. A New, Stereospecific Chloroepoxide Synthesis

Sir:

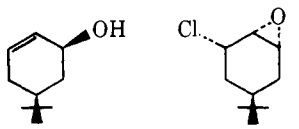
We wish to report our discovery of an unusual neighboring group involvement by hydroxyl during the halogenation of 2-cycloalkenols. This new allylic alcohol-to-haloepoxide transformation, exemplified by the oxidation of **1** to **3** with *tert*-butyl hypochlorite, documents the first case we know of a conceptually simple anchimeric participation in hydroxyhalonium ions such as **2**. We disclose in this com-



1 2 (X = Cl) 3 (X = Cl)

munication compelling evidence for the intermediacy of **2** and related species derived from **7** and **8**, whose cyclization to haloepoxides is powerfully controlled by clearly defined conformational and stereochemical requirements.

Although neighboring group participation by adjacent oxygen functions has been well documented in the solvolytic reactions of halides and sulfonate esters,[1] we were surprised to find no literature reports of such effects in the halogenation of allylic alcohols. In fact our preliminary studies with cyclohexenols **1**[2] and **4** revealed that trans Br_2 addition by a variety of brominating agents occurred to the exclusion of any intramolecular process.[3] Even though entropy factors are clearly favorable for closure of a three-membered ring, any participation of the adjacent hydroxyl would apparently require sources of X^+ having a nonnucleophilic counterion. *tert*-Butyl hypochlorite (*t*-BuOCl) is among the simplest of such reagents[4] and is known to undergo ionic additions to alkenes[5] and dienes.[6] Indeed, when **1** was stirred with 2 equiv of *t*-BuOCl in CCl_4 at room temperature for 12 h, a major product was isolated (45%) having spectral characteristics (NMR δ ($CDCl_3$) 0.87 (s, 9 H), 3.39 (m, 2 H), 4.15 (broad m, 1 H); mass spectrum (chemical ionization) *m/e* 188 (M^+), 173) indicative of secondary chloride and oxirane functionality. That this product was purely the *trans*-chloroepoxide **3** (matching spectra) could be demonstrated by comparison with authentic samples of both isomers **3** and **5**, prepared by straightforward methods[7,8] and easily distinguishable by gas chromatography. No other oxirane or carbonyl-containing substances were present in the product mixture. As anticipated, the isomeric pseudoequa-



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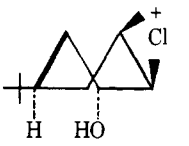
torial cyclohexenol **4** prepared by reduction of the corresponding enone (diisobutylaluminum hydride) afforded numerous uncharacterized products of halogenation but *no chloroepoxides* under identical reaction conditions. Other results indicate the absence of anchimeric participation in *t*-BuOCl oxidations of similar equatorial cyclohexenols to be characteristic.[11]

Since its discovery we have sought to answer some of the mechanistic questions raised by this remarkable chloroepoxide synthesis. Foremost, *t*-BuOCl oxidation of **1** is unaffected by changes in solvent ($CHCl_3$, hexane) and proceeds equally smoothly in the presence or absence of light, as well as atmospheric oxygen. Although a simple bimolecular radical mechanism cannot be ruled out, no bromoepoxides are formed when **1** is exposed to *t*-BuOBr, a reagent known to effect facile free-radical halogenations.[12] An alternative mechanism involves chlorine transfer to produce an allylic hypochlorite, then closure to **3**. This proposal does not easily explain the observed stereochemical outcome; moreover efforts to synthesize this hypohalite intermediate inevitably result in its decomposition to the corresponding ketone.

The remaining ionic pathway involving cyclization of an hydroxychloronium ion **2** is strongly supported by the following observations. At first glance participation by the neighboring hydroxyl in **2** appears to violate the well-established principle that three-membered ring systems experience trans diaxial opening.[13] In this instance the cyclic chloronium ion in question can achieve such favorable overlap with the adjacent OH only if the ring adopts a boat conformation, as in **6**. To test this point, an analogous pseu-



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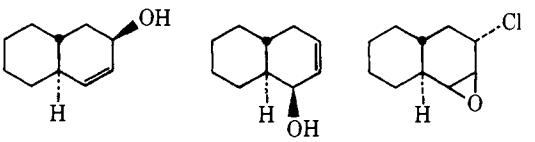
doaxial cyclohexenol **7**,[2] *whose trans-ring fusion precludes the key boat shift* was exposed to *t*-BuOCl. Principally ketonic substances were produced, and a thorough product examination unearthed no oxirane-containing compounds. Yet **8**,[14] an allylic isomer of **7** *which can achieve the proper boat conformation.* did form a chloroepoxide **9** with *t*-BuOCl, albeit in low (10%) yield (NMR δ 3.10 (broad s, 1 H), 3.40 (d, 1 H, J = 6 Hz), 4.25 (broad m, 1 H); mass spectrum (CI) M^+ 186; identity with an authentic sample prepared from **12**[7b] confirmed by VPC coinjection). Addi-



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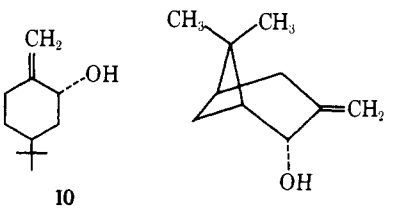
tional evidence for an ionic mechanism may be gathered from experiments with **10** and with *trans*-pinocarveol, **11**.[16] In both cases oxidation with *t*-BuOCl follows substantially the same course as molecular bromination, with Wagner-Meerwein shifts affording a variety of rearranged products.



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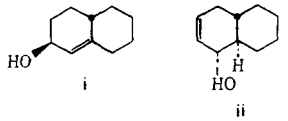
In conclusion it is clear that these unique stereospecific transformations, which we liken in part to iodolactonization,[17] provide further compelling support for the principle of diaxial attack in alkene additions and the chemistry of three-membered rings.

Acknowledgment. It is a pleasure to acknowledge stimulating conversations about this work with Professor Albert Eschenmoser of the E.T.H. (Zurich) during his term as Debye Lecturer at Cornell. The author thanks Dr. J. Henion for his expert assistance in obtaining mass spectral information, also Professors J. K. Crandall and B. Rickborn for kindly supplying samples of pinocarveol and octalol **7**. Finally, acknowledgment is made to the Research Corpora-

tion and to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for their support of this research.

References and Notes

(1) For a good review see (a) E. S. Gould, "Mechanism and Structure in Organic Chemistry", Holt, Rinehart, Winston, New York, N.Y., 1959, pp 561–570; (b) B. Capon, *Q. Rev., Chem. Soc.*, **18**, 45–111 (1964).
(2) B. Rickborn and R. P. Thummel, *J. Org. Chem.*, **34**, 3583 (1969).
(3) Since the inception of our work a report has appeared describing the bromination of cycloalkenols: P. L. Barili, G. Bellucci, G. Berti, M. Golfarini, F. Marioni, and V. Scartoni, *Gazz. Chim. Ital.*, **104**, 107 (1974). These workers have confirmed many of our own early results.
(4) Molecular iodine also meets these requirements; however, we could induce no reaction with **1**.
(5) C. F. Irvin and G. F. Hennion, *J. Am. Chem. Soc.*, **63**, 858 (1941).
(6) (a) W. Oroshnik and R. A. Mallory, *J. Am. Chem. Soc.*, **72**, 4608 (1950); (b) B. Ganem and V. R. Small, Jr., *J. Org. Chem.*, **39**, 3728 (1974), and other unpublished results.
(7) Structure **3** was prepared in two different ways: (a) by chlorination of **4** ($SOCl_2$, CCl_4) and subsequent epoxidation (*m*-chloroperoxybenzoic acid, CH_2Cl_2), or (b) by stereospecific epoxidation[9] of **1** (*m*-chloroperoxybenzoic acid, benzene), then mesylation and displacement by chloride.[10]
(8) Compound **5** was synthesized by chlorination of **1** (Cl_2, CCl_4, 0 °C) then cyclization in base of the resulting dichloroalcohol (sodium isopropoxide, isopropyl alcohol).
(9) H. B. Henbest, *Proc. Chem. Soc., London*, 159 (1963).
(10) G. Stork, P. A. Grieco, and M. Gregson, *Tetrahedron Lett.*, 1393 (1969).
(11) Equatorial cyclohexenols we have examined include Δ^1- and Δ^4-cholesten-3β-ol as well as octalols *i* and *ii*.



Although we have not studied hypohalite additions to acyclic alcohols in detail, we have observed that allyl alcohol itself undergoes an explosive 1,2 addition with *t*-BuOCl. No epichlorohydrin is thereby generated.
(12) C. Walling and A. Padwa, *J. Org. Chem.*, **27**, 2976 (1962).
(13) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis", Wiley Interscience, New York, N.Y., 1967, pp 99–102.
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(17) J. K. Crandall and L. C. Crawley, *J. Org. Chem.*, **33**, 2375 (1968).
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Aliphatic Hydroxylation via Oxygen Rebound. Oxygen Transfer Catalyzed by Iron

Sir:

There has been continued intense interest in the mechanism of action of heme-containing hydroxylases and the nature of reactive intermediates in these systems.[1] Two of the more important aspects of enzymic hydroxylation yet to be fully explained are oxygen transfer without equilibration with water and oxidation with net retention of configuration at the functionalized carbon (Scheme I).

Basic to the understanding of such processes is a catalog of the chemistry intrinsic to the higher oxidation state iron complexes (**1**) which have been implicated in these reactions.[2] We report here a single, nonenzymic oxidation, catalyzed by iron, that reveals both of these features.

Recent developments in our laboratories have provided evidence that modified Fenton's reagent systems (Fe^{2+}–H_2O_2–CH_3CN) produce an iron-bound oxidant, not free hydroxyl radical, that responds to substituent derived directive effects.[3] We have also detailed a photolytic entry to this reactive intermediate which revealed the sensitivity of the observed regioselectivity to changes in conformational equilibria.[4]

Table I. Peroxyacid–Ferrous Ion Induced Hydroxylation of Cyclohexanol

	Diol					
Peracid	*cis*-1,2	*trans*-1,2	*cis*-1,3	*trans*-1,3	*cis*-1,4	*trans*-1,4
CF_3CO_3H[a]	32	25	30	7	2	5
MCPBA[a]	37[b]	37	19	2.4	2.2	2.2
CH_3CO_3H[a]	7	16	36	20	4	18

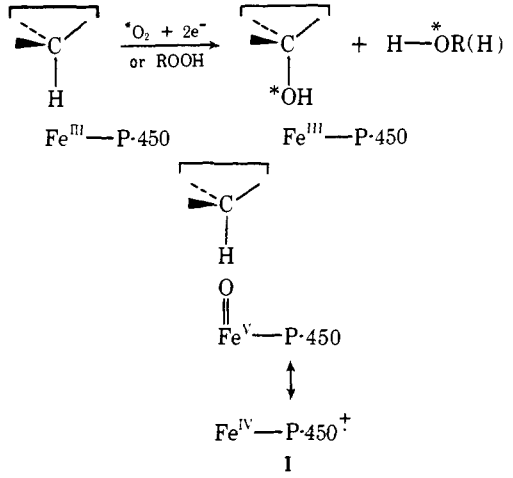
[a] Results for addition of 10 mmol of peracid in 10 ml of CH_3CN to 10 mmol of $Fe(ClO_4)_2 \cdot 6H_2O$ and 10 mmol of cyclohexanol in 60 ml of CH_3CN at 0 °C. Products were analyzed as we have previously described (cf. ref 3). All data are typical of multiple runs. [b] Diol yield 9%; cyclohexanone 40%; recovered cyclohexanol 50%.

Table II. Mass Spectra of *cis*- and *trans*-1,2-Cyclohexanediol (**2** and **3**) (Relative Intensities)[f]

m/e	120	119	118	117	116	101	100	99	98
2				8.7	100				160
3				8.7	100				160
a			7.8	100	7.1		9.7	125.6	34.4
b			8.3	100	33.7		12.9	131.4	71.4
c			8.3	6.6	100		4.2		108
d			10.8	6.8	100		9.4		110
e	3.9	41.5	5.3	9.9	100	50.1			122

[a] **2** from MCPBA–Fe $(ClO_4)_2$ oxidation of *trans*-2-deuteriocyclohexanol, $D_0/D_1 = 0.07$. [b] **3** from *trans*-2-deuteriocyclohexanol, $D_0/D_1 = 0.34$. [c] **2** from MCPBA–$Fe(ClO_4)\cdot 11H_2{}^{18}O$ (54% enrichment) oxidation of cyclohexanol, $^{18}O/^{16}O = 0.083$. [d] **3** from MCPBA–$Fe(ClO_4)_2\cdot 11H_2{}^{18}O$ (54% enrichment), $^{18}O/^{16}O = 0.108$. [e] **2** and **3** from cyclohexanol–2,2,6,6-cyclohexanol-d_4 (1:1.35), $D_3/D_0 = 0.415$. [f] All data are typical of multiple runs.

Scheme I



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We have now examined the hydroxylation of cyclohexanol by ferrous ion–peroxyacid systems with startling and revealing results.[5] Thus, addition of an acetonitrile solution of *m*-chloroperbenzoic acid (MCPBA) to cyclohexanol–ferrous perchlorate in acetonitrile at 0 °C led to the formation of cyclohexanone (40%) and all possible cyclohexanediols (9%).[6]

Critical to the understanding of the mechanism of this hydroxylation and any relationships with biological processes is identification of the source of the new hydroxyl oxygen. We have explored this question by mass spectral examination of the isotopic content of the product diols isolated from an oxidation of cyclohexanol by MCPBA and ferrous perchlorate undecahydrate ($H_2{}^{18}O$, 54% enrichment). Surprisingly, the $^{18}O/^{16}O$ ratios for *cis*- and *trans*-1,2-cyclohexanediol (**2** and **3**) were found to be only 0.08 and 0.1, respectively (Table II).